

SUMMARY AND CONCLUSION

The thesis entitled “**FORMULATION DEVELOPMENT AND EVALUATION OF ANTIHISTAMINE, DECONGESTANT DRUGS AND THEIR COMBINATIONS**” is divided into 5 chapters.

Chapter 1 deals with introduction where in details of the allergic inflammation of nasal airways and orodispersible tablets ,chewable tablet and bilayer extended tablets advantages and disadvantages have been highlighted.

Allergic rhinitis is an allergic inflammation of nasal airways. It occurs when an allergen, such as pollen, dust or animal dander is inhaled by an individual with a sensitized immune system. The allergen triggers the production of antibody immunoglobulin E (IgE), which binds to mast cells and basophils containing histamine. Histamines produce increased vascular permeability, causing fluid to escape from capillaries into tissues, which leads to the classic symptoms of an allergic reaction: - a runny nose and watery eyes. Antihistamines suppress the histamine-induced wheal response (swelling) and flare response (vasodilation) by blocking the binding of histamine to its receptors on nerves, vascular smooth muscle, glandular cells, endothelium, and mast cells. They exert a competitive antagonism to histamines.

Orally disintegrating tablets or orodispersible tablets are uncoated tablets intended to be placed in the mouth where they disperse rapidly before being swallowed. They disintegrate within three minutes. These tablets combine the advantage of both liquid and conventional tablet formulations allowing the ease of swallowing the drug in the form of liquid dosage form. Chewable tablets are required to be broken and chewed in between the teeth before ingestion. Ideally

chewable formulations have smooth texture upon disintegration, pleasant taste and no bitter or unpleasant after taste . Bi-layer tablets can be primary option to avoid chemical incompatibilities between APIs by physical separation and to enable the development of different drug release profiles. Bi-layer tablet is suitable for sequential release of two drugs in combination and also for sustained release of tablet in which one layer is for immediate release as loading dose and second layer is maintenance dose (Alderborn G, *et al*, 1982)

The present work Loratadine was chosen as the model antihistaminic drug. Loratadine ($C_{22}H_{23}C_1N_2O_2$) is a derivative of Azatadine and a second-generation histamine H_1 receptor antagonist used in the treatment of allergic rhinitis and Urticaria. Loratadine competes with free histamine and exhibits specific, selective peripheral H_1 antagonistic activity. This blocks the action of endogenous histamine, which subsequently leads to temporary relief of the negative symptoms (e.g. nasal congestion, watery eyes) brought on by histamine. Loratadine belongs to BCS class II, (Low solubility and High permeability), hence to improve the solubility micronized drug was used for the study.

Phenylephrine hydrochloride is a selective α_1 -adrenergic receptor agonist used primarily as a decongestant, as an agent to dilate the pupil, and to increase blood pressure. Phenylephrine decreases nasal congestion by acting on α_1 -adrenergic receptors in the arterioles of the nasal mucosa to produce constriction. This leads to decreased edema and increased drainage of the sinus cavities. It belongs to BCS class I (High solubility and High permeability) and due to its shorter half-life of 2.1 to 3.4 hours, it is usually formulated into an extended release dosage form.

Chapter 2 details about the literature review of allergic inflammation, orodispersible tablets, chewable tablets, bilayer extended tablets and review of Loratadine & phenylephrine are also presented.

Chapter 3 deals with scope and objectives of the study was to formulate and evaluation of various dosage forms like orally disintegrating tablets (ODT), chewable tablets and bilayer tablets for different age group of patients like children, geriatric patients and adults containing an antihistaminic drug and nasal decongestant drug which was intended for treatment of allergic rhinitis. The work plan included:

The main objectives of the present study are:

- To design and develop orodispersible tablets, chewable tablets and bilayered tablets for the widely used anti-allergic drug, Loratadine and phenylephrine using suitable super disintegrants and special tablet excipients.
- To carry out preformulation studies on the selected drug and excipients.
- To carry out physico-chemical evaluation tests for the granules of the formulations developed such as bulk density, tapped density, compressibility index, Hausner's ratio and angle of repose.
- To carry out physico-chemical evaluation tests for the formulations developed such as thickness, hardness, weight variation test, dispersion test, disintegration test and drug content uniformity.
- To study the *in vitro* drug release studies using suitable dissolution apparatus.
- To perform stability studies for the selected best formulations as per ICH Guidelines to be performed.

Chapter 4 deals with materials and methods. The complete list of materials, chemicals, equipments and instruments used for the present studies has been listed. The methodology of research has been described

Formulation and Evaluation of orally disintegrating tablets of Loratadine

Loratadine (micronised) was received from Rolabo SL, Micro crystalline cellulose (FMC Biopolymers), Pearlitol 200SD and Pearlitol flash (Roquette), Croscarmellose Sodium (AcDi-Sol SD-711) from FMC Biopolymers, Starch 1500 LM (Colorcon), Maltodextrin like Glucidex IT 12 (Roquette), Citric acid, Sodium bicarbonate, Colloidal silicon dioxide, Aspartame, Mint flavour, Sodium stearyl fumarate were of pharmaceutical grade.

Preparation of Loratadine orally disintegrating tablets

The orally dispersible tablet of Loratadine was prepared using micro crystalline cellulose as diluent and binder, Pearlitol 200SD as directly compressible diluent, croscarmellose Sodium as super disintegrant and Starch 1500LM as binder and disintegrant, Maltodextrin (Glucidex IT 12) as diluent, Citric acid as salivating agent, colloidal silicon dioxide as glidant, aspartame as sweetener, mint flavour as flavouring agent, sodium stearyl fumarate as lubricant. All ingredients except colloidal silicon dioxide, aspartame, mint flavour, sodium stearyl fumarate were shifted and mixed in an octagonal blender for 15 minutes. Aspartame, mint flavour and colloidal silicon dioxide were shifted and added to above blend and mixed for 5 minutes. Finally the blend was lubricated using sodium stearyl fumarate and compressed by using 8 mm flat punches with break line on upper punch and plain on lower punch in Kambert eight station rotary compression machine to produce ODT tablets.

Preformulation studies

Loratadine along with different excipients were subjected to accelerated stress conditions after preparing the drug and excipients admixtures and evaluated by using Differential scanning calorimeter (Mettler Toledo DSC1 Star System). The drug- excipients ratios will vary for diluents, disintegrants, binders, lubricants and sweeteners present in the formulation. Results indicated that there was no incompatibility of following excipients with Loratadine.

Evaluation of tablets

Friability test, hardness, drug content, measurement of liquid uptake, water absorption ratio, disintegration time, dissolution studies.

Stability studies

Optimized formulation was subjected to short term accelerated stability studies at $40 \pm 2^\circ\text{C}$ and $75 \pm 5\%$ RH and $25 \pm 2^\circ\text{C}$ and $60 \pm 5\%$ RH for six months testing.

Formulation and Evaluation of chewable tablets of Loratadine

Loratadine (micronised) was procured from Matrix Labs, India, co-processed microcrystalline cellulose and guar gum (Avicel CE 15) from FMC Biopolymers USA, Mannitol (Pearlitol 25C) and maize Starch from Roquette France, ethyl cellulose (Ethocel Std 10FP) from colorcon, povidone K-30 from ISP, citric acid from Kinsun International China, raspberry flavour from Givaudan UK Ltd, Aspartame from Manus Aktteva, India, colloidal silicon dioxide from Cabot Sanmar Ltd India, Magnesium stearate from Ferro Portugal were of pharmaceutical grade.

Preformulation studies

Preformulation studies were carried out for Loratadine and the probable excipients used in the development of this formulation. The Loratadine was mixed with the

individual excipient as per the predetermined ratio and each admixture was filled in glass vial and closed with a rubber stopper and aluminium seal. These vials were charged in stability at Stress condition like 40⁰ C / 75 % RH and room temperature of 25⁰ C/ 60 % RH for a period of one month. Similarly the API was also kept in these two conditions in similar way. The samples were observed for any physical change in 15 days and in 30 days. The initial samples were subjected to differential scanning calorimeter and the results obtained showed no significant shift in the melting point of these drugs thereby ruling out incompatibility of these drugs with excipients.

Preparation of Loratadine chewable tablets

Chewable tablets containing Loratadine 5 mg were prepared by selecting the excipients used in pre-formulation studies. The chewable tablet of Loratadine was prepared by using aqueous wet granulation technique with micro crystalline cellulose, lactose monohydrate and Mannitol as diluents. Ethyl cellulose as polymer for taste masking. Povidone and maize starch as binder. Apart from this we have used flavours like raspberry and aspartame as sweetener. Citric acid is used as taste enhancer. Pharma grade colours are used like D&C Yellow No 10, FD&C Yellow No.6 and FD &C Red No 40 as colours. Sodium starch glycolate as disintegrant, colloidal silicon dioxide and magnesium stearate as glidant and lubricant respectively.

Evaluation of chewable tablets

- a) Micromeritic properties of the blend
- b) Hardness
- c) Weight variation
- d) Drug content

- e) Friability
- f) *In vitro* drug release studies.

Formulation design and evaluation of Loratadine and extended release

Phenylephrine hydrochloride tablets

Loratadine (ZydusCadila), anhydrous lactose (Pharmatose DCL 21) from DMV, microcrystalline cellulose (Avicel PH102) from FMC Biopolymer, pregelatinized starch (Starch 1500) from Colorcon, magnesium stearate from Ferro Corporation. Phenylephrine Hydrochloride (Divi's Lab), microcrystalline cellulose (Avicel PH 101) from FMC Biopolymer, dicalcium phosphate dihydrate (Calipharm D) from Innophose, hydroxy propyl methylcellulose (Methocel K15M) from Colorcon, hydroxyethyl cellulose Natrosol 250 L from Ashland, iron oxide red, colloidal silicon dioxide (Aerosil 200 pharma) from Evonik, stearic acid (Speziol L2SM Pharma) from Cognis and Opadry clear YS-IR-7006 from Colorcon.

Preformulation studies

The drug along with the excipients was subjected to pre-formulation studied by mixing the drug and the excipients in different ratios of their composition to study the compatibility of drug with excipients. The mixture was mixed and packed in glass vial and closed with rubber closure and sealed with Aluminium cap and subjected to accelerated condition at 40°C and 75% RH for 1 month and observed for any physical changes like colour and appearance etc. The initial samples were subjected to differential scanning calorimeter and the results obtained showed no significant shift in the melting point of these drugs thereby ruling out incompatibility of these drugs with excipients.

Preparation of immediate release layer of Loratadine

All the ingredients were weighed according to the formula. The Loratadine, lactose, Avicel Ph102, and PG Starch were passed through sieve#30 and blended in an octagonal blender (Garson's Ltd) for 20 minutes, then magnesium Stearate was passed through sieve #60 and lubrication was done for the blend for five minutes.

Preparation of phenylephrine HCl sustained release layer

Phenylephrine HCl sustained release layer was prepared by wet granulation method according to the formula. All the intra-granular ingredients were passed through sieve#30 separately, weighed and mixed in geometrical order. Then HPMC K15 or Natrosol 250L was dispersed in required amount of purified water along with iron oxide red and wet granulation was done. The granules obtained were dried until the required LOD was reached. Then the granules were passed through sieve #20 and pre-lubricated with aerosil which was passed through sieve#40 and blended for 10mins in the blender. Granules were lubricated for 5 minutes with magnesium stearate which was passed through sieve#60. Then the tablets were compressed using caplet shape punches on 10 station bilayer tablet compression machine Mini Press II MTDL (Karnavati).

Compression of tablets

The tablets were compressed using Cadmach bilayer compression machine. The extended release layer of phenylephrine HCl was compressed first followed by immediate release layer of Loratadine. The Bilayer tablets were film coated with Opadry clear YS-IR-7006 supplied by Colorcon up to weight gain of 10mg per tablet in an automatic coating machine (Neocota).

The film coating of bilayer tablet provided better appeal and gloss to the tablet increasing the aesthetic appearance of the tablet.

Evaluation

- a) Micromeritic properties of the blend
- b) Hardness
- c) Weight variation
- d) Drug content
- e) Friability
- f) Disintegration test for immediate release part.
- g) *In vitro* dissolution studies

Chapter 5 deals with a detailed account of results with corresponding interpretation and discussion on the outcome of each phase of experimentation.

Formulation and Evaluation of orally disintegrating tablets of Loratadine

The growing importance of orally dispersible tablets was under lined recently when European Pharmacopoeia adopted the term “orodispersible tablets” and given the limit as 3min for dispersion in the mouth, when taken orally. These above formulations being prepared by direct compression method is versatile and simple and very easy to process. The results are very promising with respect to release profiles and disintegration time within limits. The formulation of orally disintegrating tablets mainly depends on the type of super disintegrants used like croscarmellose Sodium (Ac-Di-Sol SD-711) and PEARLITOL flash, a combination of mannitol and Starch used as direct compressible diluent along with sodium bicarbonate and citric acid showed good results with 99.98% drug content, 35 Seconds disintegration time, 0.13% friability and 99 % drug release in 10 minutes along with very good mouth feel. The absorption maximum (λ) for

Loratadine was found to be 278 nm in simulated gastric fluid. Standard calibration curve of Loratadine was measured in simulated gastric fluid and was found to be linear with correlation coefficient being 0.9997. In trial 005 where the increased disintegration time and the wetting time was observed with increased quantity of Maltodextrin. The compressed tablets showed less weight variation with standard deviation of 1.16 in trial 005 being the maximum amongst all the trials. In trial 009 overall results including drug release and weight variation was found to be good and satisfying all the criteria for an Orally disintegrating tablets. All the above nine formulations were prepared and evaluated. The dissolution data reveals that drug release was within acceptable limits. The *in vitro* dissolution profiles of trial 005, trial 007 and trial 009 comparing the best release profiles amongst the three excipients like maltodextrin (Glucidex IT 12), mannitol (Pearlitol 200SD) and pearlitol flash respectively. The incorporation of pearlitol flash, sodium bicarbonate along with citric acid showed very fast disintegration with less friability and good hardness.

Formulation and evaluation of chewable tablets of Loratadine

The tablets were prepared by wet granulation method. The different excipients were tested for their compatibility with Loratadine, which revealed that there was no chemical and physical interactions occurred, which was evident by DSC thermal analysis graphs. The pre-formulation parameters such as bulk density, tapped density, compressibility index and Hausner's ratio were analysed for prepared blend before compression. The thickness, hardness, friability, weight variation and drug content uniformity was also evaluated for prepared tablets. From all obtained results, it was found that the trials 3,4, 5 & 6 shows slow drug release up to 60mins but trial 5 was the best one with almost 100% drug release at

the end of 60 minutes which is formulated without use of ethyl cellulose and also having 100% drug content. Hence, finally it was concluded that the trial 5 is the optimized formulation which complies all ideal characteristics of chewable tablets. The Loratadine chewable tablet with formulation trial 5 concluded the robust formula with better patient compliance and drug release.

Formulation design and evaluation of Loratadine and extended release Phenylephrine hydrochloride tablets

Loratadine and phenylephrine HCl bilayer tablets were prepared by loratadine as immediate release layer and phenylephrine HCl layer as sustained release. Loratadine immediate release layer was prepared by using lactose DCL21, avicel Ph102 as diluent, PG starch as binding agent and magnesium stearate as lubricant. Then the phenylephrine HCl sustained release layer was prepared by using dicalcium phosphate, MCC 101 as diluent, HPMC K15M, Natrosol 250L, iron oxide red, aerosil, stearic acid as lubricant. A total of six formulations were designed. As the material was free flowing, there by the tablets obtained were of uniform weight with acceptable variation as per IP specifications i.e., below 7.5%. Hardness of the tablets were found to be about 94-107N. Friability below 0.38% was an indication of good mechanical resistance of tablets. The Optimized formulation (trial 6) has shown good release mechanism for both immediate release layer of Loratadine and extended release layer of phenylephrine hydrochloride. In this formulation of (trial 6), phenylephrine HCl has shown release effectively over a period of 8 hours. The tablets containing 10 mg of Loratadine as an immediate release and 30 mg of phenylephrine HCl as sustained release will definitely be a promising formulation in comparison to conventional release product. The formulation containing 22 mg of HPMC K15M and 8 mg of

Natrosol 250L per tablet as a retarding polymer showed desirable *in vitro* kinetic properties. The extended release profile of phenylephrine HCl follows zero order kinetics by showing highest linearity and diffusion controlled mechanism following Higuchi model of drug release. This final formulation of trial No 6 provides an oral solid pharmaceutical combination comprising of non-sedative antihistamine like loratadine and decongestant like phenylephrine HCl in a bilayer tablet for treatment of allergic rhinitis in improved patient compliance.

Stability studies

The optimised formulations of different dosage forms were subjected to stability studies in order to determine physical and chemical changes of these formulations on storage. The physicochemical parameter of the optimized formulation was not changed significantly on storage. The negligible *in vitro* release changes observed before and after storage. The result indicates that the formulation was stable on the required storage conditions.

SCOPE FOR FUTURE STUDY

The present study scientifically established the formulation and evaluation of various dosage forms like orally disintegrating tablets (ODT), chewable tablets and bilayer tablets for different age group of patients like children, geriatric patients and adults containing an antihistaminic drug and nasal decongestant drug which was intended for treatment of allergic rhinitis can be further investigated on

- To be performed the bioavailability study for orodispersible tablets, chewable tablets and bilayered tablets for the widely used anti-allergic drug, Loratadine and Phenylephrine using suitable super disintegrants and special tablet excipients.
- A detailed pharmacokinetic studies for the bilayer extended release tablets.